manufacturers with their comments sheds little light on the role of nicotine in smokeless tobacco and does not significantly change the evidence in the record.

The Agency made extensive findings based on the evidence then before it regarding the statements, research, and actions of the smokeless tobacco manufacturers in the Jurisdictional Analysis. The Agency received comments on these findings from the tobacco industry, public health organizations and other groups and members of the public. After careful consideration of the evidence in the record and the public comments, the Agency finds that the evidence provides an independent basis for concluding that smokeless tobacco is in fact intended to affect the structure and function of the bodies of smokeless tobacco users.

As described in this section, the evidence from internal company documents and other sources shows that smokeless tobacco manufacturers: (1) know that nicotine has pharmacological effects and uses, including causing and sustaining addiction; and (2) manipulate and control the delivery of nicotine from smokeless tobacco in a manner that promotes tolerance and addiction in consumers. Indeed, in the case of the nation's largest smokeless tobacco manufacturer, the statements of senior officials and the company's marketing strategies reveal that the company relies on an explicit "graduation process," under which users of smokeless tobacco are encouraged to progress from "starter" products that deliver low levels of nicotine to products that deliver higher and more addictive levels of nicotine. The cumulative evidence shows that the manufacturers design smokeless tobacco with an intent to affect the structure and function of the body.[994]

[994] The discussion of the statements, research, and actions of the manufacturers in this section cites many documents. It is the totality of the evidence from these documents that the Agency relies upon. No single document cited by the Agency is essential to the Agency's conclusion that the manufacturers intend their

1. The Smokeless Tobacco Manufacturers Understand That Nicotine Has Addictive and Other Pharmacological Effects and That Consumers Use Smokeless Tobacco To Obtain these Effects

Extensive evidence in the administrative record, including statements and research of smokeless tobacco manufacturers, demonstrates that the manufacturers know that nicotine causes significant pharmacological effects, including addiction. These statements and research also demonstrate that the manufacturers understand that consumers use smokeless tobacco to obtain the pharmacological effects of nicotine.

For example, Brown & Williamson Tobacco Corporation, which is also a smokeless tobacco manufacturer,[995] understands that nicotine is addictive; that nicotine has other significant pharmacological effects; and that consumers use tobacco products to obtain nicotine. *See* section II.C.2.c., above. Researchers for Brown & Williamson's parent corporation, BATCO, have long regarded "buccal administration of nicotine" through products such as chewing tobacco and wet snuff as alternatives to the delivery of nicotine through cigarettes.[996] According to these researchers, these types of tobacco usage—smoking, chewing, and snuffing—allow nicotine to go directly into the blood and to the brain; they stated that "[t]he common factor in all the types of tobacco usage . . . is nicotine,

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products to affect the structure and function of the body. In particular, none of the documents in the Agency's docket of confidential documents is essential to the Agency's determination. *See* AR (Vols. 505-518).

[995] Valero G, Moist poised to overtake leaf; smokeless tobacco, *U.S. Distribution Journal,* Dec. 15, 1995; 222(12):12. *See* AR (Vol. 711 Ref. 22).

[996] Minutes of B.A.T. Group Research Conference at St. Adele, Quebec (Nov. 9-13, 1970), at 3. *See* AR (Vol. 44 Ref. 15-2).

either absorbed through the lungs *or the lining of the nose or mouth.* Taken in these ways *nicotine will quickly enter a direct route, in the blood, to the brain.*"[997]

Indeed, as recently as 1992, Brown & Williamson stated that "[t]he fact that people use snuff and chewing tobacco indicates that administration routes other than the inhalation route can deliver tobacco satisfaction."[998] BATCO scientists use "satisfaction" as a euphemism for the pharmacological effects of nicotine, stating "[i]ntuitively it is felt that *'satisfaction' must be related to nicotine.* Many people believe it [is] a 'whole body response' and *involves the action of nicotine in the brain.*"[999] *See* section II.E.2., below.

Similarly, a senior vice president for marketing for United States Tobacco Company (UST), the nation's largest smokeless tobacco manufacturer,[1000] wrote in a memo on new product development that "*virtually all tobacco usage is based upon nicotine, 'the kick,' satisfaction.*"[1001] The executive further stated:

> Nicotine gives the consumer satisfaction. Some would describe it as a pleasant feeling. Others would describe it as a kick. . . . Others would describe it as a relaxing feeling.[1002]

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[997] BATCO Group R&D Conference on Smoking Behaviour at Southampton, England (Oct. 11-12, 1976), at BW-W2-02145 (emphasis added). *See* AR (Vol. 14 Ref. 180-2).

[998] Transdermal Nicotine Patches, at 3. *See* AR (Vol. 531 Ref. 124).

[999] BATCO Nicotine Conference at Southampton, England (Jun. 6-8, 1984) at BW-W2-01977 (emphasis added). *See* AR (Vol. 22 Ref. 287-7).

[1000] UST has 82% of the market for moist snuff products sold in the United States in 1994. It also has nearly 40% of the market for all smokeless tobacco sold in the United States. *See* Valero G, Moist poised to overtake leaf; smokeless tobacco, *U.S. Distribution Journal,* Dec. 15, 1995; 222(12):12. *See* AR (Vol. 711 Ref. 22).

[1001] Deposition of Erik Lindqvist, transcript of jury trial proceedings at 1662 in *Marsee v. U.S. Tobacco,* Civil Action No. 84-2777R (W.D. Ok. 1986) (emphasis added). *See* AR (Vol. 22 Ref. 292).

[1002] *Id.*

Another UST document compares the nicotine delivery of one of its products, Skoal Bandits, with the nicotine delivery of cigarettes. This document states:

> The nicotine contents are more or less equivalent to that of a good quality cigarette of average strength. The nicotine is absorbed, giv[ing] satisfaction to the smoker.[1003]

Like the major cigarette manufacturers, UST has funded its own studies on nicotine pharmacology, including studies on the absorption of nicotine from snuff and chewing tobacco, the effects of smokeless tobacco on performance and psychophysiological response, and detection of nicotine in blood.[1004] Other UST studies were designed to compare routes of nicotine administration in snuff and cigarette smoking[1005] and to describe the pharmacokinetics of nicotine and its major metabolites in experienced and inexperienced snuff

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[1003] Potential Questions and Answers, submitted in *Marsee v. U.S. Tobacco,* Civil Action No. 84-2777R (W.D. Ok. 1986), at 1. *See* AR (Vol. 30 Ref. 509).

[1004] Kyerematen, GA, Dvorchik, BH, Vesell, ES, Influence of different forms of tobacco intake on nicotine elimination in man, *Pharmacology* 1983;26:205-209. *See* AR (Vol. 119 Ref. 1102).

Landers DM, Crews DJ, Boutcher SH, *et al.*, The effects of smokeless tobacco on performance and psychophysiological response, *Medicine and Science in Sports & Exercise* 1992;24(8):895-903, as cited in *Health Effects of Smokeless Tobacco: Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 144 (Nov. 29, 1994). *See* AR (Vol. 710 Ref. 4).

Allen JK, Stern JR, Harris J, *Analysis of Nicotine in Blood by HPLC with Electrochemical Detection, (Abstract),* submitted for presentation at the 10th International Symposium on Column Liquid Chromatography, San Francisco, CA (May 18-23, 1986), as cited in *Health Effects of Smokeless Tobacco: Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 144 (Nov. 29, 1994). *See* AR (Vol. 710 Ref. 4).

Baldini FD, Skinner JS, Landers DM, *et al.*, Effects of varying doses of smokeless tobacco at rest and during brief, high-intensity exercise, *Military Medicine* 1992;157:51-55, as cited in *Health Effects of Smokeless Tobacco: Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 144 (Nov. 29, 1994). *See* AR (Vol. 710 Ref. 4).

[1005] U.S. Tobacco Company, Results of Comparison of Routes of Nicotine Administration. Plaintiff's exhibit 3.28 from *Marsee v. U.S. Tobacco,* Civil Action No. 84-2777R (W.D. Ok. 1986). *See* AR (Vol. 24 Ref. 318).

takers.[1006] The study comparing routes of nicotine administration, for instance, found that smokeless tobacco can actually deliver more nicotine than cigarettes to new tobacco users, stating that "for naive tobacco users, bioavailability of nicotine is greater after snuff dipping than after cigarette smoking. . . ."[1007]

UST is also a founding member of the Council for Tobacco Research (CTR).[1008] As discussed in section II.C.2.d., above, CTR has funded many studies on behalf of its members evaluating the pharmacological effects of nicotine on the body. At least one of these studies stated that nicotine in tobacco can cause "drug addiction."[1009] As a member of the Council for Tobacco Research, UST thus had direct knowledge of the pharmacological effects and the consumer uses of nicotine.

[1006] U.S. Tobacco Company, Pharmacokinetics of Nicotine and Its Major Metabolites in Naive and Habituated Snuff Takers. Plaintiff's exhibit 3.27 from *Marsee v. U.S. Tobacco,* Civil Action No. 84-2777R (W.D. Ok. 1986). *See* AR (Vol. 24 Ref. 317).

[1007] U.S. Tobacco Company, Results of Comparison of Routes of Nicotine Administration. Plaintiff's exhibit 3.28 from *Marsee v. U.S. Tobacco,* Civil Action No. 84-2777R (W.D. Ok. 1986). *See* AR (Vol. 24 Ref. 318).

[1008] UST has been intimately connected with CTR since its inception. The minutes of the initial meeting in March 1954 of the Tobacco Industry Research Council, the predecessor of the Council for Tobacco Research, indicate that UST's president was the first vice chairman of the Council. TIRC, Report on Meeting (Mar.15, 1954). *See* AR (Vol. 301 Ref. 4393). Subsequently, UST's president served as a director of CTR from 1976 to 1984. Organization and Function of CTR (summaries of CTR meetings, 1976-1984). *See* AR (Vol. 342 Ref. 5382). Prior to 1988, UST manufactured cigarettes and was a class A member of CTR. Since 1988, UST has been a class B member of CTR. *Health Effects of Smokeless Tobacco: Hearing Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives,* 103d Cong., 2d Sess. 137 (Nov. 29, 1994). *See* AR (Vol. 710 Ref. 4).

[1009] *See, e.g.,* Svennson TH, Grenhoff J, Engberg G, Effect of nicotine on dynamic function of brain catecholamine neurons, in *The Biology of Nicotine Dependence,* eds. Bock G, Marsh J, *CIBA Foundation Symposium,* 1990;152:169-180. *See* AR (Vol. 61 Ref. 273).

Tung CS, Ugedo L, Grenhoff J, *et al.,* Peripheral induction burst firing in locus coerulus neurons by nicotine mediated via excitatory amino acids, *Synapse* 1989;4(4):313-318. *See* AR (Vol. 61 Ref. 278).

Rosecrans JA, Nicotine as a discriminative stimulus: a neurobehavioral approach to studying central cholinergic mechanisms, *J Subst Abuse* 1989;1(3):287-300. *See* AR (Vol. 59 Ref. 239).

Nicotine's pharmacological effects are also understood by Procordia A.B., the parent of Pinkerton Tobacco Company, the nation's third largest smokeless tobacco manufacturer.[1010] Through corporate subsidiaries, Procordia has extensively investigated the pharmacological effects of nicotine, including funding numerous studies on nicotine's effects on the brain.[1011]

[1010] Valero G, Moist poised to overtake leaf; smokeless tobacco, *U.S. Distribution Journal*, Dec. 15, 1995; 222(12):12. *See* AR (Vol. 711 Ref. 22).

[1011] Procordia owns two foreign smokeless tobacco manufacturers, Svenska Tobaks AB and Swedish Tobacco Co. Through Svenska Tobaks and Swedish Tobacco, Procordia funded the following studies on nicotine pharmacology:

Adem A, Jossan SS, d'Argy R, *et al.*, Distribution of nicotinic receptors in human thalamus as visualized by 3H-nicotine and 3H-acetylcholine receptor autoradiography, *J Neural Transm* 1988;73(1):77-83. *See* AR (Vol. 45 Ref. 10).

Adem A, Nordberg A, Jossan SS, *et al.*, Quantitative autoradiography of nicotinic receptors in large cryosections of human brain hemispheres, *Neurosci Lett* 1989;101(3):247-252. *See* AR (Vol. 45 Ref. 9).

Andersson. K, Eneroth P, Agnati L, Nicotine-induced increases of noradrenaline turnover in discrete noradrenaline nerve terminal systems of the hypothalamus and the median eminence of the rat and their relationship to changes in the secretion of adenohypophyseal hormones, *Acta Physiol Scand* 1981;113:227-231. *See* AR (Vol. 273 Ref. 3784).

Andersson K, Fuxe K, Agnati LF, *et al.*, Effects of acute central and peripheral administration of nicotine on ascending dopamine pathways in the male rat brain. Evidence for nicotine induced increases of dopamine turnover in various telencephalic dopamine nerve terminal systems, *Med Biol* 1981;59(3):170-176. *See* AR (Vol. 45 Ref. 11).

Andersson K, Fuxe K, Eneroth P, *et al.*, Interactions of nicotine and pentobarbitone in the regulation of telencephalic and hypothalamic catecholamine levels and turnover and of adenohypophyseal hormone secretion in the normal male rat, *Naunyn Schmiedebergs Arch Pharmacol* 1982;321:287-292. *See* AR (Vol. 423 Ref. 7141).

Andersson K, Hockey GRJ, Effects of cigarette smoking on incidental memory, *Psychopharmacology* 1977;52:223-226. *See* AR (Vol. 125 Ref. 1300).

Biber A, Scherer G, Hoepfner I, *et al.*, Determination of nicotine and cotinine in human serum and urine: an interlaboratory study, *Toxicol Lett* 1987;35(1):45-52. *See* AR (Vol. 140 Ref. 1649).

Copeland JR, Adem A, Jacob P, *et al.*, A comparison of the binding of nicotine and nornicotine stereoisomers to nicotinic binding sites in rat brain cortex, *Naunyn Schmiedebergs Arch Pharmacol* 1991;343(2):123-127. *See* AR (Vol. 152 Ref. 1887).

Falkeborn Y, Larsson C, Nordberg A, Chronic nicotine exposure in rat: a behavioral and biochemical study of tolerance, *Drug Alcohol Depend* 1981;8:51-60. *See* AR (Vol. 141 Ref. 1679).

Fuxe K, Andersson K , Eneroth P, *et al.*, Neurochemical mechanisms underlying the neuroendocrine actions of nicotine: focus on the plasticity of central cholinergic nicotinic receptors, *Prog Brain Res* 1989;79:197-207. *See* AR (Vol. 47 Ref. 95).

Fuxe K, Everitt BJ, Hokfelt T, On the action of nicotine and cotinine on central 5-hydrcxytryptamine neurons, *Pharmacol Biochem Behav* 1979;10(5):671-677. *See* AR (Vol. 152 Ref. 1869).

Fuxe K, von Euler G, Finnman UB, *et al.*, Reduction of [3 H]nicotine binding in hypothalamic and cortical membranes by dopamine D1 receptors, *Acta Physiol Scand* 1989;136(2):295-296. *See* AR (Vol. 127 Ref. 1351).

Fuxe K, Agnati LF, Jansson A, *et al.*, Regulation of endocrine function by the nicotinic cholinergic receptor, *CIBA Foundation Symposium* 1990;152:113-130. *See* AR (Vol. 131 Ref. 1450).

Grenhoff J, Aston Jones G, Svensson TH, Nicotinic effects on the firing pattern of midbrain dopamine neurons, *Acta Physiol Scand* 1986;128(3)351-358. *See* AR (Vol. 143 Ref. 1771).

Larsson C, Nordberg A, Comparative analysis of nicotine-like receptor-ligand interactions in rodent brain homogenate, *J Neurochem* 1985;45:24-31. *See* AR (Vol. 141 Ref. 1684).

Larsson C, Lundberg PA, Halen A, *et al.*, In vitro binding of 3H-acetylcholine to nicotinic receptors in rodent and human brain, *J Neural Transm* 1987;69:3-18. *See* AR (Vol. 137 Ref. 1586).

Larsson C, Nilsson L, Halen A, *et al.*, Subchronic treatment of rats with nicotine: effects on tolerance and on [3 H]acetylcholine and [3 H]nicotine binding in the brain, *Drug Alcohol Depend* 1986;17:37-45. *See* AR (Vol. 141 Ref. 1677).

Nisell M, Nomikos GG, Svensson TH, Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area, *Synapse* 1994;16:36-44. *See* AR (Vol. 276 Ref. 3870).

Nordberg A, Romanelli L, Sundwall A, *et al.*, Effect of acute and subchronic nicotine treatment on cortical acetylcholine release and on nicotinic receptors in rats and guinea-pigs, *British Journal of Pharmacology* 1989;98(1):71-78. *See* AR (Vol. 131 Ref. 1454).

Nordberg A, Wahlstrom G, Arnelo U, *et al.*, Effect of long-term nicotine treatment on [3-H]nicotine binding sites in the rats brain, *Drug Alcohol Depend* 1985;16:9-17. *See* AR (Vol. 141 Ref. 1678).

Nordberg A, Bergh C, Effect of nicotine on passive avoidance behaviour and motoric activity in mice, *Acta Pharmacol Toxicol Copenh* 1985;56(4):337-341. *See* AR (Vol. 274 Ref. 3820).

Nordberg A, Sundwall A, Pharmacodynamic effects of nicotine and acetylcholine biosynthesis, in mouse brain, *Acta Pharmacol Toxicol Copenh* 1983;52(5):341-347. *See* AR (Vol. 133 Ref. 1503).

Nordberg A, Larsson C, Studies of muscarinic and nicotinic binding sites in brain, *Acta Physiol Scand Suppl* 1980;479:19-23. *See* AR (Vol. 137 Ref. 1590).

Pilotti A, Enzell CR, McKennis H Jr, *et al.*, Studies on the identification of tobacco alkaloids, their mammalian metabolites and related compounds by gas chromatography- -Mass Spectrometry, *Beitrage zur Tabakforschung* 1976;8(6):339-349. *See* AR (Vol. 96 Ref. 704).

Furthermore, numerous studies of the pharmacological effects and chemistry of nicotine and the sites and mechanisms of nicotine receptors in the brain have been funded by the Smokeless Tobacco Research Council.[1012] The Smokeless Tobacco Research Council

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Schievelbein H, Absorption of Nicotine Under Various Conditions (an introductory review), presented at the Nicotine Workshop (Nov. 1974), *Beitrage zur Tabakforschung* 1976;8(5):196-202. *See* AR (Vol. 60 Ref. 254).

Schmiterlow CG, Hansson E, Andersson G, *et al.*, Distribution of Nicotine in the Central Nervous System, *Annals of the New York Academy of Sciences* 1967;142:2-14. *See* AR (Vol. 152 Ref. 1859).

Schmiterlow CG, Hansson E, Tissue distribution of C 14-nicotine, in Von Euler US (ed.), *Tobacco Alkaloids and Related Compounds* 1965:75-86, ed. Von Euler US. *See* AR (Vol. 60 Ref. 256).

Siegel RA, Andersson K, Fuxe K, *et al.*, Rapid and discrete changes in hypothalamic catecholamine nerve terminal systems induced by audiogenic stress, and their modulation by nicotine-relationship to neuroendocrine function, *Eur J Pharmacol* 1983;91:49-56. *See* AR (Vol. 60 Ref. 262).

Svensson TH, Engberg G, Effect of nicotine on single cell activity in the noradrenergic nucleus locus coerulus, *Acta Physiol Scand Suppl* 1980;479:31-34. *See* AR (Vol. 422 Ref. 7124).

Szuts T, Olsson S, Lindquist NG, *et al.*, Long-term fate of [14C]nicotine in the mouse: retention in the bronchi, melanin-containing tissues and urinary bladder wall, *Toxicology* 1978;10(3):207-220. *See* AR (Vol. 131 Ref. 1458).

[1012] Anand R, and Lindstrom J, Chromosomal localization of seven neuronal nicotinic acetylcholine receptor subunit genes in humans, in *Report of the Council for Tobacco Research - USA, Inc. 1992*, at 101. *See* AR (Vol. 465 Ref. 7874).

Bencherif M, Lukas RJ, Cytochalasin modulation of nicotinic cholinergic receptor expression and muscarinic receptor function in human TE671/RD cells: a possible functional role of the cytoskeleton, *Journal of Neurochemistry* 1993;61(3):852-864. *See* AR (Vol. 141 Ref. 1683).

Britto LRG, Keyser KT, Lindstrom JM, *et al.*, Immunohistochemical localization of nicotinic acetylcholine receptor subunits in the mesenchephalon and diencephalon of the chick (Gallus Gallus), *The Journal of Comparative Neurology* 1992;317:325-340. *See* AR (Vol. 131 Ref .1453).

Cholerton S, McCracken NW, Idle JR, Sources of inter-individual variability in nicotine pharmacokinetics, in *Nicotine and Related Alkaloids: Absorption, Distribution, Metabolism, and Excretion*, eds. Gorrod JW, and Wahren J (1993), at 219-253. *See* AR (Vol. 47 Ref. 70).

Gerzanich V, Anand R, Lindstrom J, Homomers of $\alpha 8$ and $\alpha 7$ subunits of nicotinic receptors exhibit similar channel but contrasting binding site properties, *Molecular Pharmacology* 1994;45(2):212-220. *See* AR (Vol. 276 Ref. 3861).

Hsu YN, Amin J, Weiss D, *et al.*, Chronic nicotine exposure decreases the activation of $\alpha 4\beta 2$ but not $\alpha 3\beta 2$ neuronal nicotinic receptors expressed in *xenopus* oocytes, in *International Symposium on Nicotine: The*

Effects of Nicotine on Biological Systems II, eds. Clarke PBS *et al.* (Montreal: Jul. 21-24, 1994). *See* AR (Vol. 135 Ref. 1529).

Keyser KT, Britto LRG, Schoepfer R, *et al.*, Three subtypes of α-bungarotoxin - sensitive nicotinic acetylcholine receptors are expressed in chick retina, *Journal of Neuroscience*, Feb. 1993;13(2):442-454. *See* AR (Vol. 126 Ref. 1343).

Marks R, Lindstrom J, Schroder H, Cellular and subcellular visualization of the β2 - subunit of the nicotinic acetylcholine receptor in the mouse cerebral cortex, in *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II*, eds. Clarke, PBS, *et al.*, at session 1, 4 (Montreal: Jul. 21-24, 1994). *See* AR (Vol. 104 Ref. 952).

McFarland BJ, Seidler FJ, Slotkin TA, Inhibition of DNA synthesis in neonatal rat brain regions caused by acute nicotine administration, *Developmental Brain Research* 1991;58:223-229. *See* AR (Vol. 414 Ref. 6940).

McLane DE, Wu X, Schoepfer R, *et al.*, Identification of sequence segments forming the α-bungarotoxin binding sites on two nicotinic acetylcholine receptor α subunits from the avian brain, in *Report of the Council for Tobacco Research - USA, Inc. 1991. See* AR (Vol. 19 Ref. 195-22).

McLane DE, Wu X, Lindstrom JM, *et al.*, Epitope mapping of polyclonal and monoclonal antibodies against two α-bungarotoxin-binding α subunits from neuronal nicotinic receptors, in *Report of the Council for Tobacco Research - USA, Inc. 1992. See* AR (Vol. 19 Ref. 195-23).

Navarro HA, Seidler FJ, Schwartz RD, *et al.*, Prenatal exposure to nicotine impairs nervous system development at a dose which does not affect viability or growth, *Brain Research Bulletin* 1989;23:187-192. *See* AR (Vol. 137 Ref. 1585).

Nelson S, Shelton GD, Lei S, *et al.*, Epitope mapping of monoclonal antibodies to *torpedo* acetylcholine receptor γ subunits, which specifically recognize the ε subunit of mammalian muscle acetylcholine receptor, in *Report of the Council for Tobacco Research - USA, Inc. 1992. See* AR (Vol. 19 Ref. 195-23).

Seeman JI, Secor HV, Armstrong DW, *et al.*, Enantiomeric resolution and chiral recognition of racemic nicotine and nicotine analogues by β-cyclodextrin complexation. Structure-enantiomeric resolution relationships in host-guest interactions, *Analytical Chemistry* 1988;60:2120-2127. *See* AR (Vol. 275 Ref. 3836).

Slotkin TA, Cho H, Whitmore WL, Effects of prenatal nicotine exposure on neuronal development: selective actions on central and peripheral catecholaminergic pathways, *Brain Research Bulletin* 1987;18(5):601-611. *See* AR (Vol. 137 Ref. 1573).

Slotkin TA, Navarro HA, McCook EC, *et al.*, Fetal nicotine exposure produces postnatal up-regulation of adenylate cyclase activity in peripheral tissues, *Life Sciences* 1990;47:1561-1567. *See* AR (Vol. 276 Ref. 3865).

Slotkin TA, Lappi SE, Tayyeb MI, *et al.*, Chronic prenatal nicotine exposure sensitizes rat brain to acute postnatal nicotine challenge as assessed with ornithine decarboxylase, *Life Sciences* 1991;49(9):665-670. *See* AR (Vol. 137 Ref. 1580).

Slotkin TA, Developmental effects of nicotine, in *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II*, eds. Clarke PBS, *et al.*, at session 4, S15 (Montreal: Jul. 21-24, 1994). *See* AR (Vol. 60 Ref. 264).

was formed by the major smokeless tobacco manufacturers to fund scientific studies on behalf of the manufacturers. One such study recognized that nicotine is "*the major pharmacologically active component of tobacco.*"[1013]

2. The Smokeless Tobacco Manufacturers Manipulate Nicotine Deliveries from Smokeless Tobacco in a Manner That Promotes Tolerance and Addiction in Users

The evidence in the record also demonstrates that smokeless tobacco manufacturers manipulate the nicotine delivery of their products to produce graduated deliveries of nicotine that promote tolerance and addiction. Specifically, the evidence shows that the nicotine deliveries of smokeless tobacco are manipulated so that products intended for new users deliver low amounts of nicotine, while products intended for experienced users deliver far higher amounts of nicotine. This manipulation of nicotine delivery is accomplished primarily

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Slotkin TA, Lappi SE, Seidler FJ., Impact of fetal nicotine exposure on development of rat brain regions: critical sensitive periods or effects of withdrawal?, *Brain Research Bulletin* 1993;31:319-328. *See* AR (Vol. 137 Ref. 1571).

Wahlsten JL, Lindstrom JM, Conti-Tronconi BM, Amino acid residues within the sequence region α55-74 of torpedo nicotinic acetylcholine receptor interacting with antibodies to the main immunogenic region and with snake α-neurotoxins, in *Report of the Council for Tobacco Research - USA, Inc. 1993*, at 166-167. *See* AR (Vol. 465 Ref. 7873).

Wahlsten JL, Lindstrom JM, Ostlie N, *et al.*, Myasthenia gravis: effect on antibody binding of conservative substitutions of amino acid residues forming the main immunogenic region of the nicotinic acetylcholine receptor, in *Report of the Council for Tobacco Research - USA, Inc. 1993*, at 166. *See* AR (Vol. 465 Ref. 7873).

Yu CI, Morgan DG, Wecker L, Northern blot analysis demonstrates the presence of three different transcripts of neuronal nicotinic acetylcholine receptor α4 gene in rat brain, in *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II*, eds. Clarke PBS, *et al.*, at session 2, P10 (Montreal: Jul. 21-24, 1994). *See* AR (Vol. 104 Ref. 952).

[1013] Cholerton S, McCracken NW, Idle JR, Sources of inter-individual variability in nicotine pharmacokinetics, in *Nicotine and Related Alkaloids: Absorption, Distribution, Metabolism, and Excretion*, eds. Gorrod JW, Wahren J (1993):219-253, at 219 (emphasis added). *See* AR (Vol. 47 Ref. 70).